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## **Bayesian reconstruction of the insulin secretion rate**

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# Bayesian Reconstruction of the Insulin Secretion Rate

*Cobal 2*

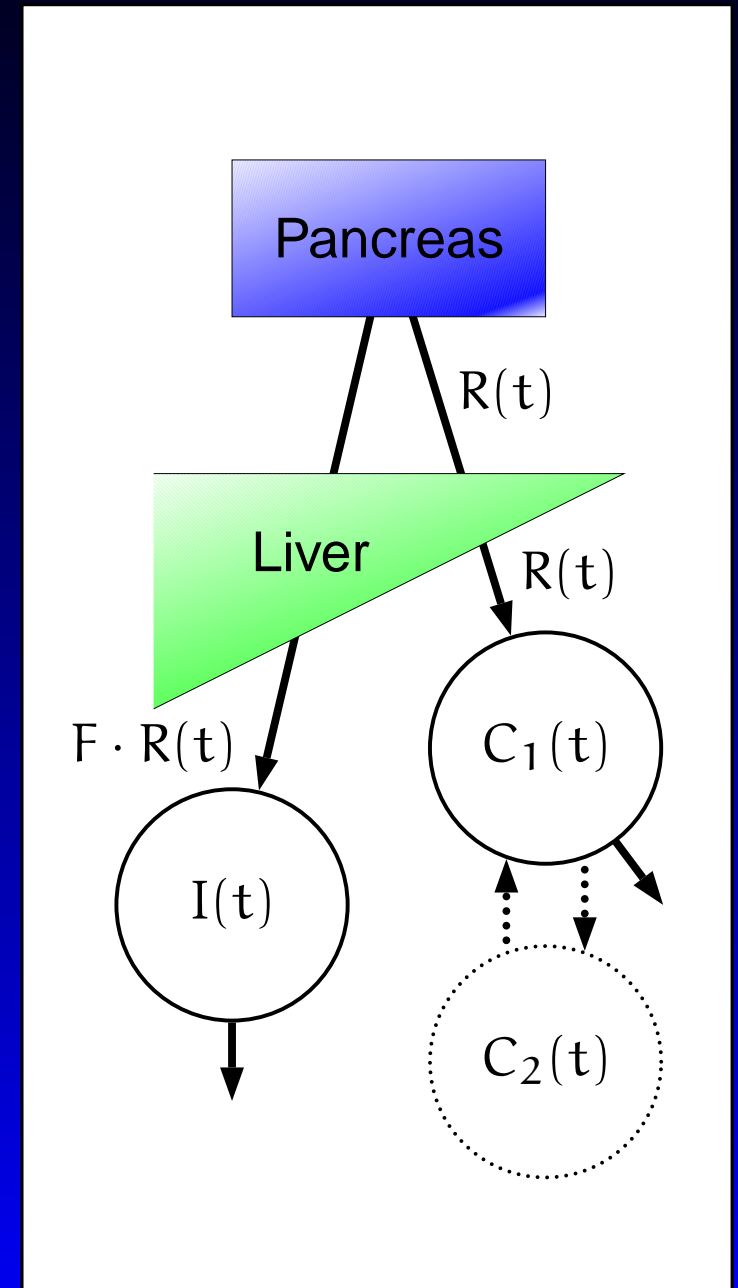
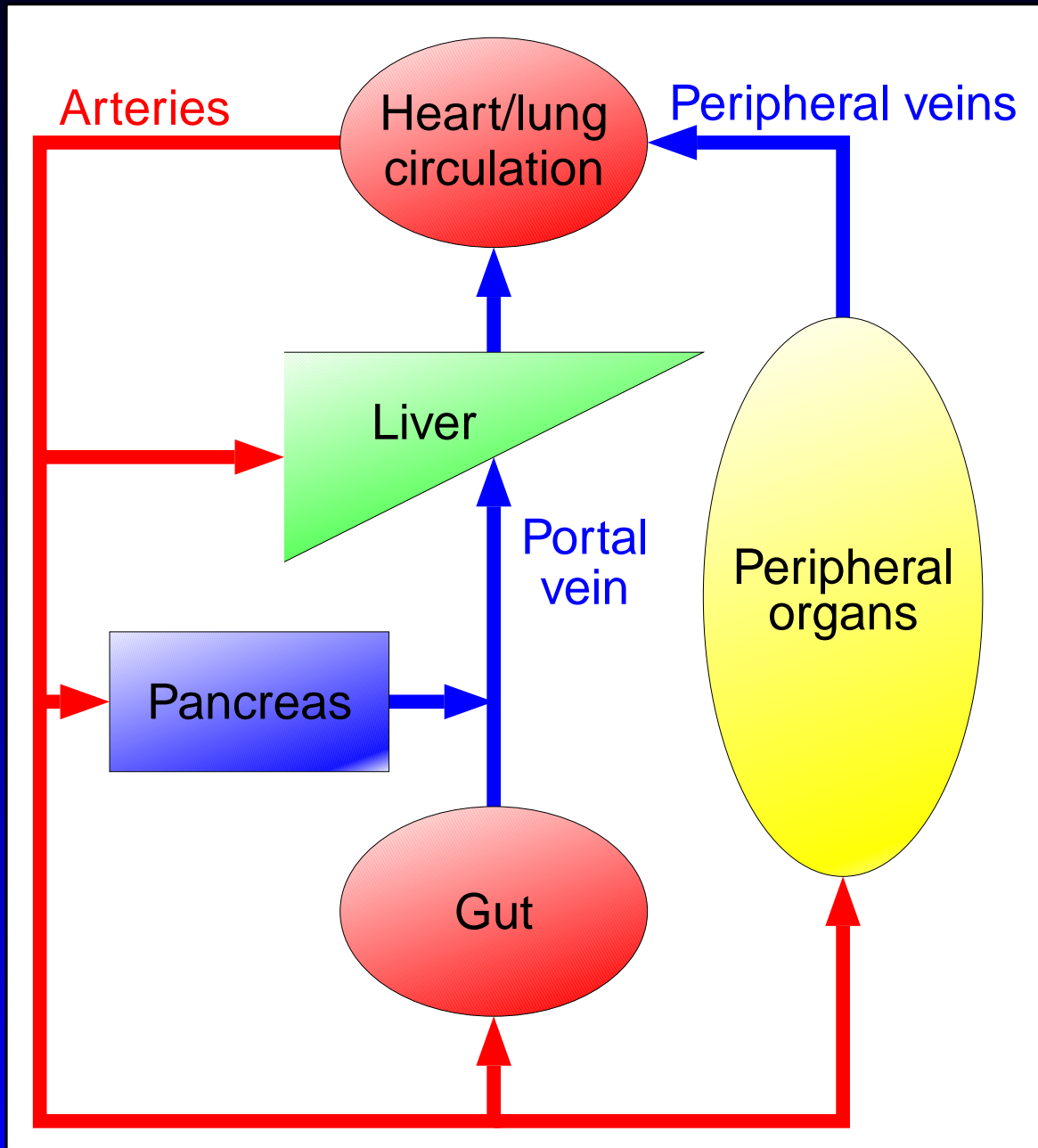
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# Physiological Circulation



# Aim

Determine the Insulin Secretion Rate (**ISR**) allowing for

- a quantitative understanding of the glucose regulating system
- an evaluation of the therapeutic effect of e.g. a **new** diabetic agent

# Problem

Endogenous insulin undergoes a **large** and **variable** liver **extraction**

# Fortunately

C-peptide is co-secreted on a equimolar basis and is (almost) NOT extracted by the liver

# Solution

Base assessment of ISR upon C-peptide

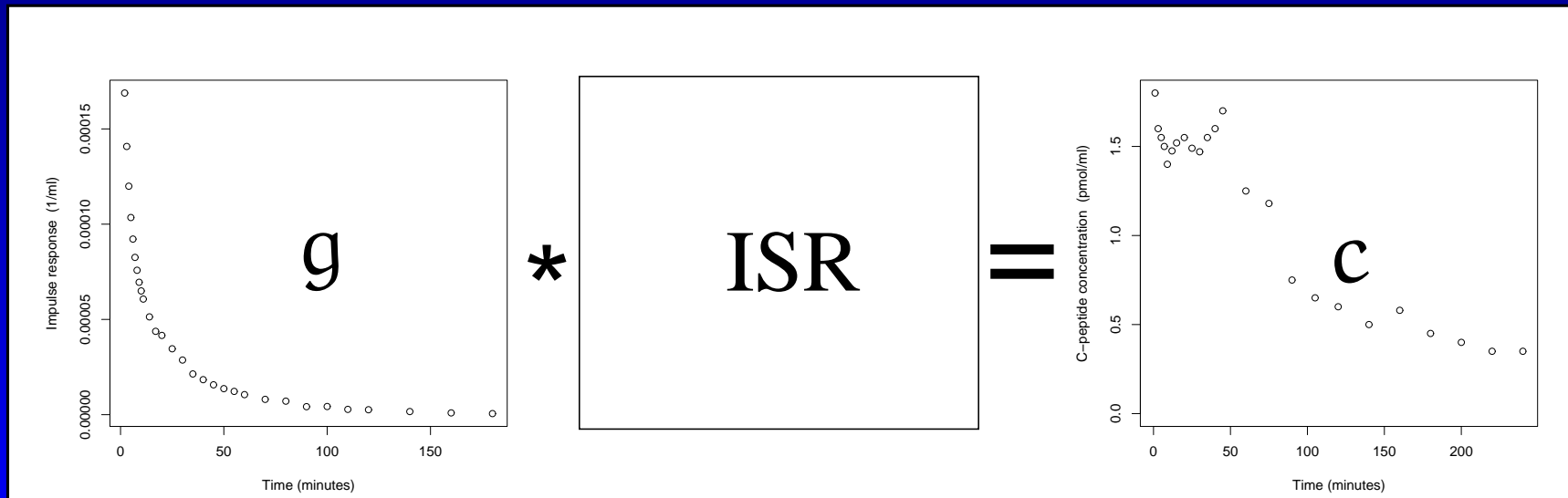
# Mathematical Convolution Model vs Data

Let

- $ISR(t)$  denote the insulin secretion rate [pmol/min]
- $c(t)$  denote the C-peptide concentration [pmol/ml] ← IVGTT
- $g(t)$  denote the C-peptide impulse response [ $ml^{-1}$ ] ← C-peptide bolus

then it is possible to relate the unmeasurable  $ISR(t)$  with  $c(t)$  by the convolution integral

$$c(t) = \int_{-\infty}^t g(t - \tau) ISR(\tau) d\tau$$



# Current Two Stage Approaches

## Main assumptions:

### Stage 1

- Imposing a sum of exponentially decaying functions  $g(t) = \sum_{i=1}^N A_i e^{-\alpha_i t}$  on the C-peptide impulse response – treated as known

### Stage 2

- Assuming ISR to be piecewise constant

## Consequence:

Leads to an ill-posed inversion problem, which can be solved through proper regularisation

$$\arg \min_{c \in \mathcal{C}} \|c_{\text{obs}} - c\|^2 + \alpha \|c\|^2$$

In a stochastic setup this may be done by the use of the variance of  $c$

# Our Approach

## Main idea:

- Consider both set of data **simultaneously**
  - unified approach
  - allowing for random deviations in e.g. the C-peptide impulse response

## Solution strategy:

- Obtain flexible class of representations of  $c(t)$  and  $ISR(t)$
- Determine their convolution properties
- Recast the problem in a Bayesian setting

## In practice:

- Rescaled phasetype densities

# Phasetype Distributions

## Definition:

Let  $T$  denote the convergence time for a Markov chain, then  $T$  has density

$$g(t) = \alpha e^{Tt} t$$

where

- $\alpha = (\alpha_1, \dots, \alpha_n)$  is an  $n$ -dimensional **row-vector** with  $\alpha_i \geq 0$  and  $\sum_{i=1}^n \alpha_i = 1$
- $T$  is an  $n \times n$  **intensity matrix** with  $T_{ii} \leq 0$  and  $T_{ij} \geq 0$  subject to  $\sum_{j=1}^n T_{ij} \leq 0$
- $t = -Te$

## Examples:

- Exponential
- Erlang
- Gaussian

## Fundamental properties:

- Dense in the space of distributions

Scaled phasetype densities



# Closed Form Convolution Models

## Assumptions:

Assume that both  $g(t)$  and  $ISR(t)$  are of scaled phasetype, i.e.

- $g(t) = \kappa_g \alpha_g e^{T_g t} t_g$
- $ISR(t) = \kappa_{ISR} \alpha_{ISR} e^{T_{ISR} t} t_{ISR}$

then the convolution  $g * ISR$  is also of scaled phasetype

- $c(t) = (g * ISR)(t) = \kappa_c \alpha_c e^{T_c t} t_c$

where

- $\kappa_c = \kappa_g \kappa_{ISR}$
- $\alpha_c = (\alpha_g, 0)$
- $T_c = \begin{bmatrix} T_g & T_g e \alpha_{ISR} \\ 0 & T_{ISR} \end{bmatrix}$

Solving the *direct* problem is **well-posed**

# Statistical Model and Algorithm

## Model:

Let

- $t_1^c, \dots, t_n^c$  denote the time points used for sampling the C-peptide
- $t_1^g, \dots, t_m^g$  denote the time points used for sampling the impulse response
- Gaussian IID distributed with variance  $\sigma_c^2$  and  $\sigma_g^2$

Thus

$$\begin{aligned} c^o(t) &\sim \mathcal{N}(c(t), \sigma_c^2), & t = t_1^c, \dots, t_n^c \\ g^o(t) &\sim \mathcal{N}(g(t), \sigma_g^2), & t = t_1^g, \dots, t_m^g \end{aligned}$$

## Naïve algorithm:

- ➊ Simulate  $g(t)$  and  $c(t)$  for initial  $\mathbf{B}_g = (\kappa_g, \boldsymbol{\alpha}_g, T_g, \sigma_g^2)$  and  $\mathbf{B}_{\text{ISR}} = (\kappa_{\text{ISR}}, \boldsymbol{\alpha}_{\text{ISR}}, T_{\text{ISR}}, \sigma_c^2)$
- ➋ Propose new candidates  $\mathbf{B}'_g$  and  $\mathbf{B}'_{\text{ISR}}$
- ➌ Evaluate new candidates according to some object function  $\pi$
- ➍ Accept or reject new candidates according to simple rule
- ➎ Goto ➋

# Likelihood Construction

## Data:

Let  $\Phi_c = (c^o(t_1^c), \dots, c^o(t_n^c))$  and  $\Phi_g = (g^o(t_1^g), \dots, g^o(t_m^g))$  denote the observed data

## Likelihood:

The likelihood function is given by

$$L(\mathbf{B}_{\text{ISR}}, \mathbf{B}_g | \Phi_c, \Phi_g) \propto \frac{\exp\{-V(\mathbf{B}_{\text{ISR}}, \mathbf{B}_g) - W(\mathbf{B}_g)\}}{\sigma_c^n \sigma_g^m}$$

where the potentials are given by

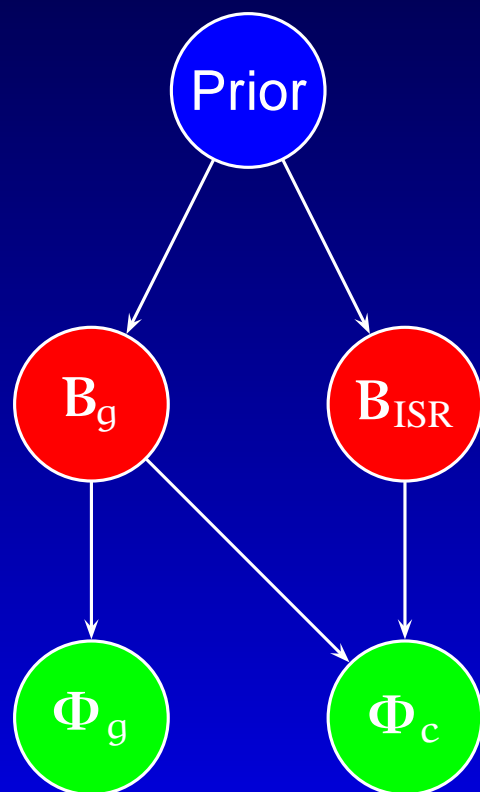
$$V(\mathbf{B}_{\text{ISR}}, \mathbf{B}_g) = \sum_{i=1}^n [c^o(t_i^c) - c(t_i^c)]^2 / 2\sigma_c^2$$

and

$$W(\mathbf{B}_g) = \sum_{i=1}^m [g^o(t_i^g) - g(t_i^g)]^2 / 2\sigma_g^2$$

# Graphical Model and Bayesian Analysis

Graphical Model:



Posterior  $\pi$ :

$$\pi(\mathbf{B}_{\text{ISR}}, \mathbf{B}_g \mid \Phi_c, \Phi_g) \propto L(\mathbf{B}_{\text{ISR}}, \mathbf{B}_g \mid \Phi_c, \Phi_g) p(\mathbf{B}_{\text{ISR}}, \mathbf{B}_g)$$

where the prior distribution is given by

$$\begin{aligned} p(\mathbf{B}_{\text{ISR}}, \mathbf{B}_g) = & p(\kappa_{\text{ISR}}) \\ & \times p(\alpha_{\text{ISR}}) \\ & \times p(\mathbf{T}_{\text{ISR}}) \\ & \times p(\kappa_g) \\ & \times p(\alpha_g) \\ & \times p(\mathbf{T}_g) \\ & \times p(\sigma_c^2) \\ & \times p(\sigma_g^2) \end{aligned}$$

Uniform

Inverse gamma

# ISR Reconstruction in Details

## Blocked Random Walk Metropolis–Hastings Updating:

Random walks are used as proposals, i.e.

$$\mathbf{T}' \sim \mathcal{N}(\mathbf{T}, \sigma_{\mathbf{T}}^2)$$

$$\boldsymbol{\alpha}' \sim \mathcal{N}(\boldsymbol{\alpha}, \sigma_{\boldsymbol{\alpha}}^2)$$

Reversible by design

$$\kappa' \sim \mathcal{N}(\kappa, \sigma_{\kappa}^2)$$

## Allowable Configurations:

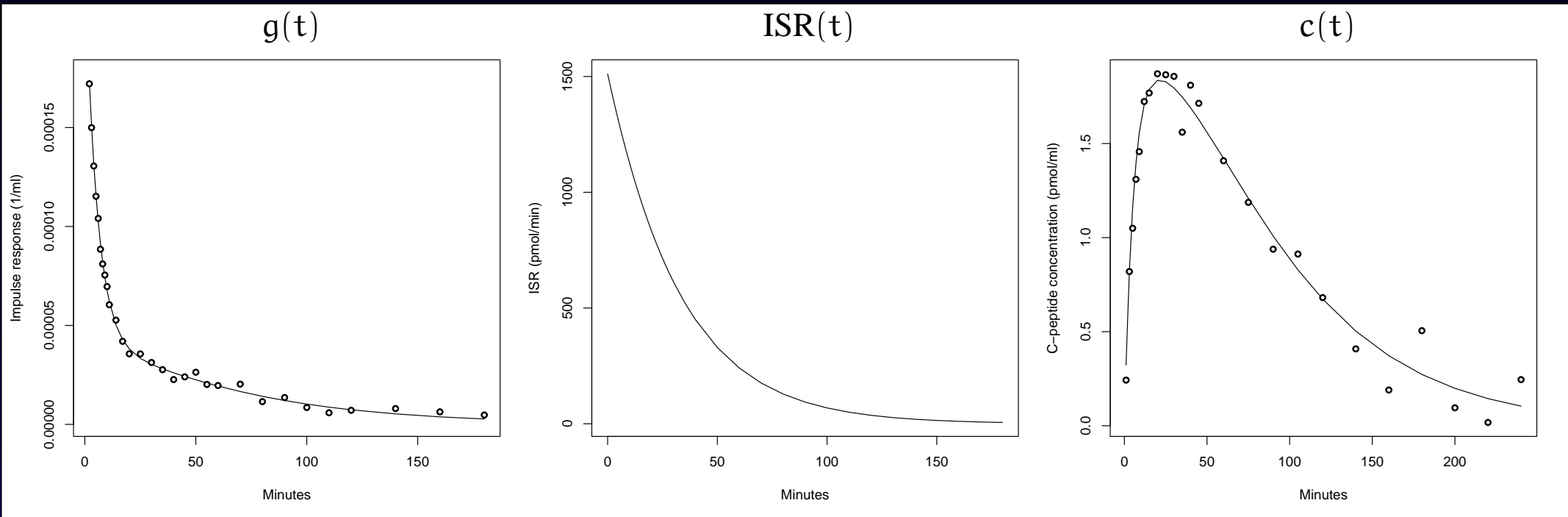
Let  $\Psi_{\mathbf{T}}$  and  $\Psi_{\boldsymbol{\alpha}}$  denote the set of allowable matrices and vectors, i.e. the validity of the state  $\mathbf{B} = (\kappa, \boldsymbol{\alpha}, \mathbf{T})$  is given by the indicator

$$1(\mathbf{B}) = 1(\kappa > 0, \boldsymbol{\alpha} \in \Psi_{\boldsymbol{\alpha}}, \mathbf{T} \in \Psi_{\mathbf{T}})$$

The proposal  $(\mathbf{B}'_g, \mathbf{B}'_{\text{ISR}}) = (\kappa'_g, \boldsymbol{\alpha}'_g, \mathbf{T}'_g, \kappa'_{\text{ISR}}, \boldsymbol{\alpha}'_{\text{ISR}}, \mathbf{T}'_{\text{ISR}})$  is then accepted with

$$\alpha = 1(\mathbf{B}'_g)1(\mathbf{B}'_{\text{ISR}}) \min \left( 1, \exp \left\{ V(\mathbf{B}_{\text{ISR}}, \mathbf{B}_g) - V(\mathbf{B}'_{\text{ISR}}, \mathbf{B}'_g) + W(\mathbf{B}_g) - W(\mathbf{B}'_g) \right\} \right)$$

# Simulation Study



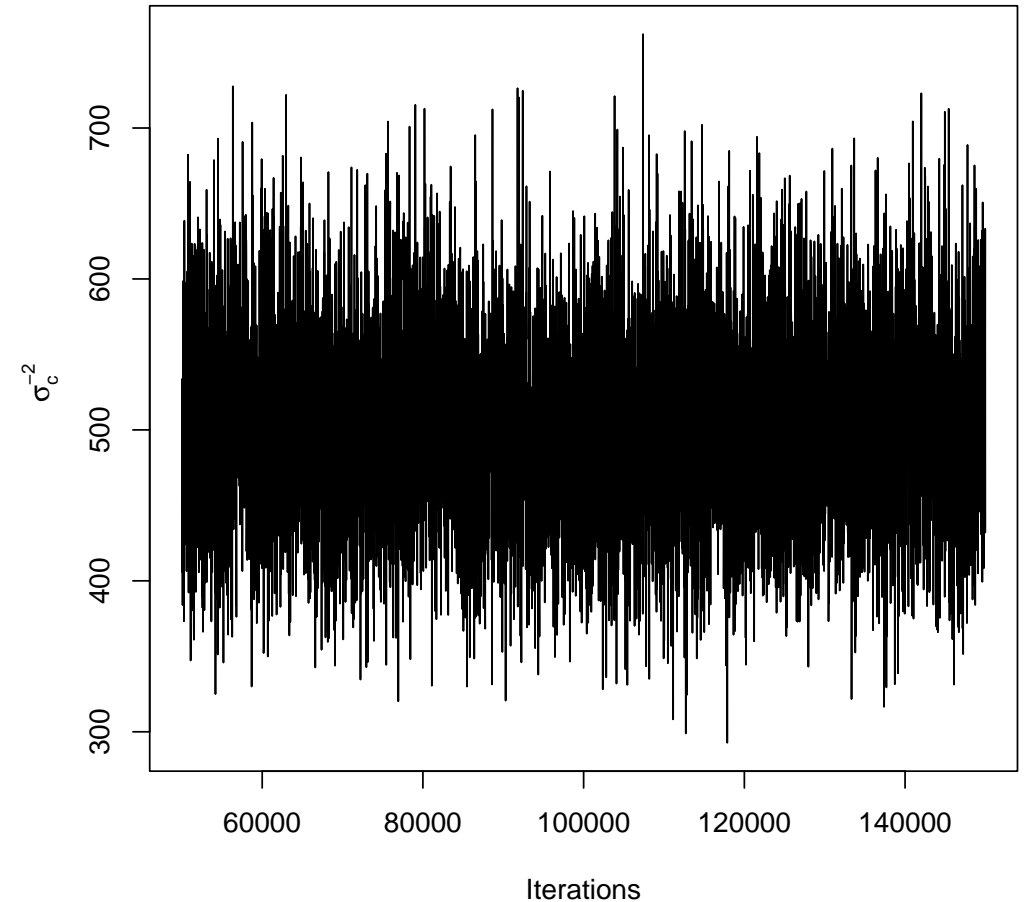
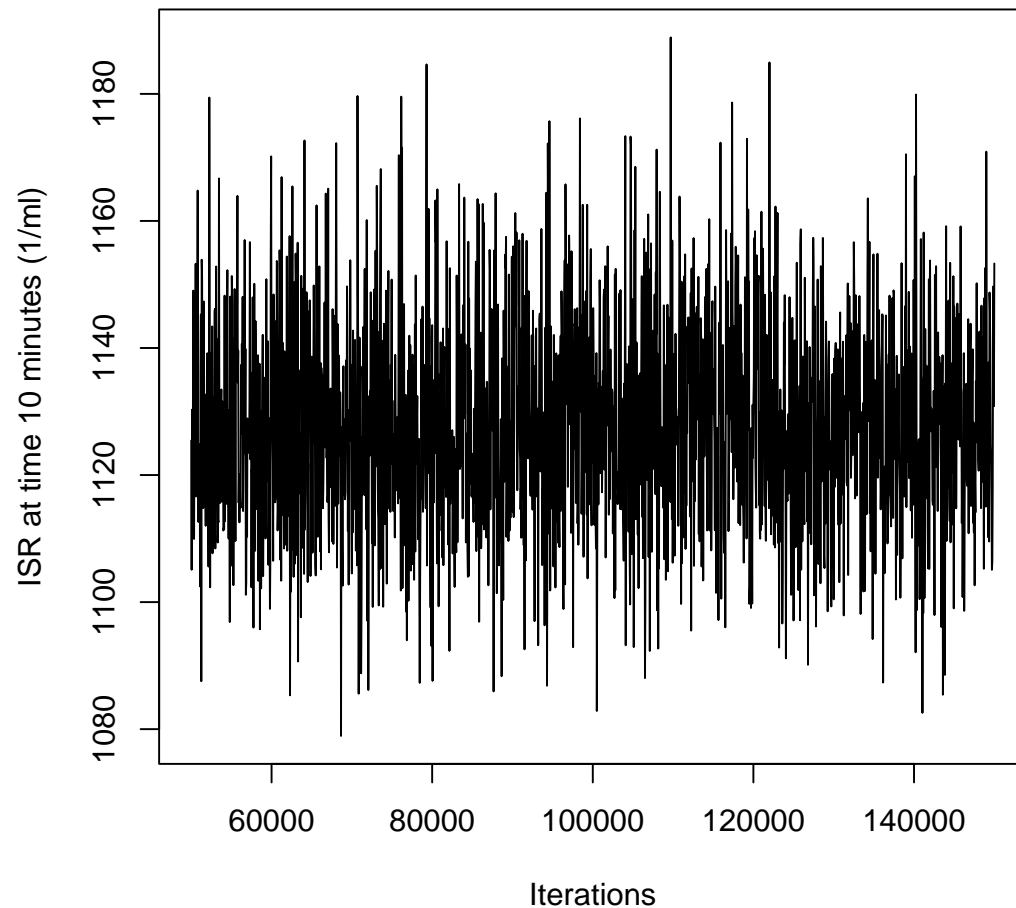
## Modifications

- ❶ Let  $V(\mathbf{B}_{\text{ISR}}, \mathbf{B}_g) \equiv 0$  to obtain good starting values for  $\mathbf{B}_g$
- ❷ Keep  $\mathbf{B}_g$  fixed and let  $W(\mathbf{B}_g) \equiv 0$  to obtain good starting values for  $\mathbf{B}_{\text{ISR}}$
- ❸ With good initial values for  $\mathbf{B}_{\text{ISR}}$  and  $\mathbf{B}_g$  a final run for 150 000 iterations is conducted

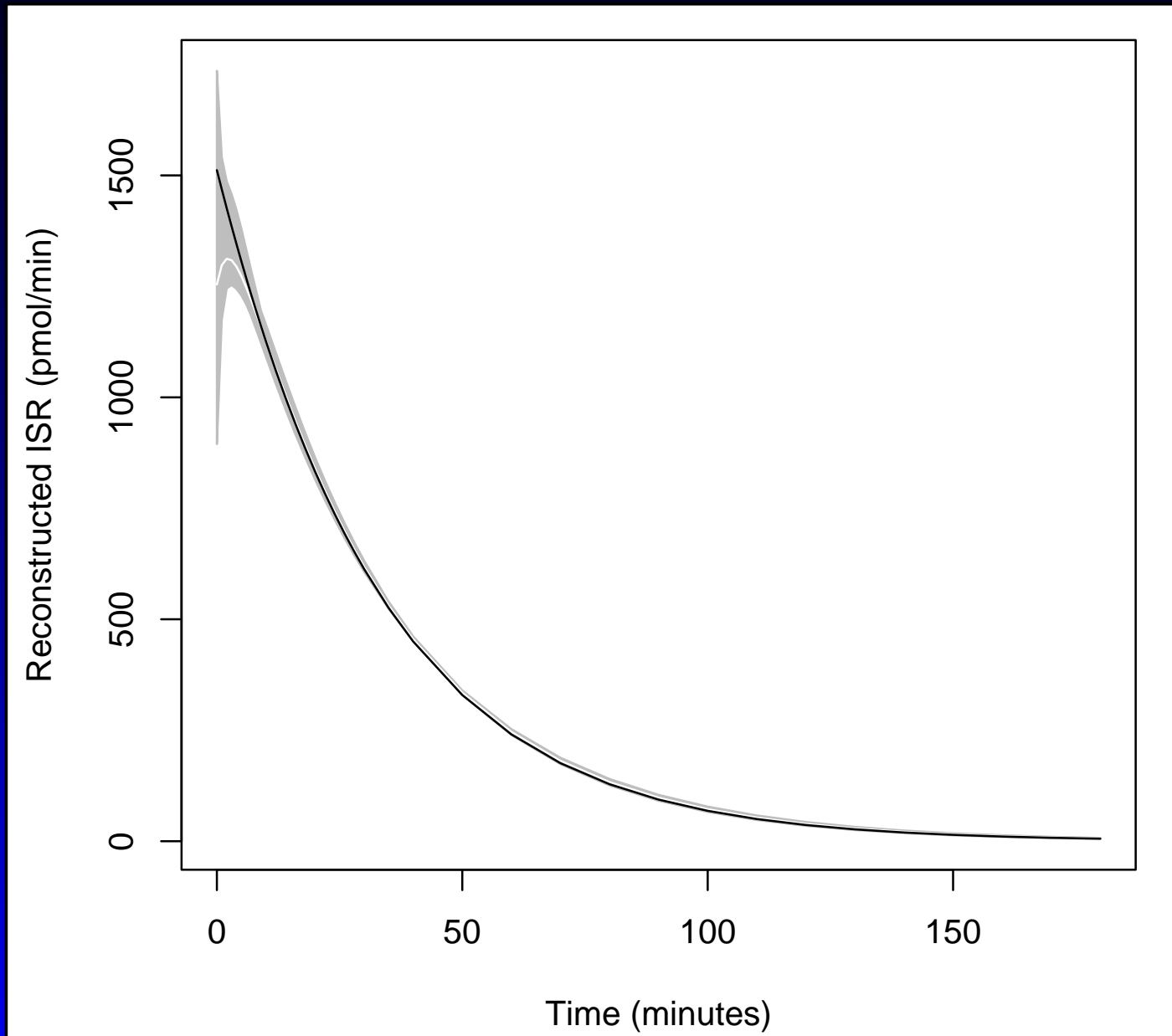
# Results

## Trace plots:

It is meaningless to trace the parameters as they have no physiological interpretation.



# Reconstructed Insulin Secretion Rate





# The NN1998 AERx Study

## Inhaled Insulin Agent:

How much of an **inhaled** insulin agent reaches the **bloodstream** ?

## Approach:

### *Experiment 1:*

- Perform traditional **C-peptide bolus experiment** followed by an **IVGTT**

### *Experiment 2:*

- Perform another IVGTT in which **inhaled insulin** is administered

>From the two experiments, we may

- ➊ Determine the subjects endogenous insuline secretion rate
- ➋ Determine both the endogenous and exogenous insulin
- ➌ Subtract to find exogenous insulin

All done  
simultaneously

# Discussion

## Pros:

- Unified approach
- Possible to make closed form reconstruction of the ISR
- Quick

## Cons:

- Problems with dimensionality (RJCMC)
- Would be slow!

## Future:

- Consider gamma densities as basis functions
- Convolution results in Kummer functions (confluent hypergeometric functions)
- Less 'nice' mathematical representation
- Computationally more tractable